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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,065	09/30/2003	A. Robin Poole	079328-0105	1202

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,065	POOLE, A. ROBIN	
	Examiner	Art Unit	
	Hope A. Robinson	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/12/06.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21,26,29,32,35,38-43,48-53,58-63,68,69 and 93-95 is/are pending in the application.

4a) Of the above claim(s) 6-21,26,29,32,35,38-43,48-53,58-63,94 and 95 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,68,69 and 93 is/are rejected.

7)☒ Claim(s) 2-5 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 30 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed December 8, 2005 on July 12, 2006 is acknowledged.

Claim Disposition

2. Claims 1-21, 26, 29, 32, 35, 38-43, 48-53, 58-63, 68-69 and 93-95 are pending. Claims 93-95 have been added. Claims 1-5, 68-69 and 93 are under examination as they relate to SEQ ID NO:3. Claims 94-95 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Note that claims 94-95 are directed to a method and the elected invention is the peptide, thus these claims would have been subjected to a restriction requirement if they were submitted at the time of filing.

Withdrawn-Specification Objection

3. Previous objection to the specification is withdrawn by virtue of submission of an amendment.

Withdrawn-Objection to Sequence Compliance

4. Previous objection to the sequences on page 9 of the specification is withdrawn by virtue of arguments presented on pages 10-11 of the response.

Maintained-Oath/Declaration

5. The Oath/Declaration remains objected to because of the following informalities:

The oath/declaration remains objected to because non-initialed and/or non-dated alterations have been made to the oath or declaration (see inventor Robin Poole). See 37 CFR 1.52(c).

Correction is required.

Withdrawn-Claim Objections

6. Previous objection to claim 69 is withdrawn by virtue of submission of an amendment.

New-Claim Objection

7. Claims 1-5, 68-69 and 93 objected to because of the following informalities:

Claim 1 is objected to because the claim should recite, "and" between items (h) and (i) or proper Markush language.

Claim 1-5 are objected to because the claims recite non-elected sequences.

Claims 2-5 are objected to because the article "An" is recited instead of "The", for example, "The isolated or purified peptide of claim 1...".

Claims 68-69 and 93 are objected to because the claims depend from non-elected claims and are not further limiting.

Correction is required.

Maintained-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 68-69 and 93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to an isolated or purified peptide (SEQ ID NO:3), that has at least 80% or at least 90% sequence identity to the peptide as claimed. The claims encompass a genus of variants that are highly variable. A skilled artisan cannot envision the detailed chemical structure for all the variants encompassed in the claim.

The specification fails to provide a representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus of peptides could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed peptides encompasses widely variant species. As such, neither the description of the structure and function of SEQ ID NOS: 3, for example, "80% sequence identity to SEQ ID NO:3 and is effective in decreasing the rate of degradation of type II collagen or the rate of chrondrocyte hypertrophy is sufficient to be representative of the attributes and features of the entire genus.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 68-69 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the proteins set forth in SEQ ID NO: 3, does not reasonably provide enablement for any peptide having at least 80% or 90% sequence homology to SEQ ID NO: 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples;. Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of peptide variants of the sequences set forth in SEQ

ID NO: 3. No correlation is made between structure and function of the claimed peptides. The claims are directed to "an amino acid sequence set forth in SEQ ID NO:3 (as elected) and 80 or 90% sequence identity to SEQ ID NO:3 which encompasses any fragment or variant thereof for the structure. There is no indication in the claims where in the sequence changes will occur to construct said variant or whether function will be retained, or be different or is nonfunctional. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. In the instant application, the partial structure in the form of the recited percent identity is insufficient to determine a chemical structure for the variants encompassed in the claims. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Therefore, the claims encompass variants that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of

475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants of the peptides. The claims broadly read on any

variant thereof for the given sequence (SEQ ID NO: 3). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, absent direction/guidance regarding whether the structure of the peptide can tolerate the modifications contemplated a non-functional protein may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed

invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Withdrawn-Claim Rejections - 35 USC ∋ 112

10. Previous rejection to claims under 35 U.S.C. 112, second paragraph, is withdrawn by virtue of submission of an amendment.

Maintianed-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 69 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Qvist et al. (U.S. Patent No. 6,110,689, August 29, 2000), based on the open language in the claim which reads on all of SEQ ID NO:3 embedded in a longer sequence.

Qvist et al. teach a sequence that is 100% identical to the peptide sequence set forth in SEQ ID NO: 3 of the instant application (see the alignment). Although, Qvist et al. do not expressly teach the function recited in the claim, the claimed invention is anticipated as the structure is disclosed and the function is an inherent property. Therefore, the limitations of the claims are met by this reference.

12. Claims 1, 68-69 and 93 are rejected under 35 U.S.C. 102(b) as being anticipated by Shriners Hospitals for Crippled Children (WO94/14070, 1994), cited on IDS filed April 30, 2004 based on the open language in the claim which reads on all of SEQ ID NO:3 embedded in a longer sequence.

Shriners Hospitals for Crippled Children teach a sequence that is 100% identical to the peptide sequence set forth in SEQ ID NO: 3 of the instant application (see the alignment). Shriners Hospitals for Crippled Children also teach a method of measuring collagen (i.e., type I-III) degradation and ways to alter same (see abstract and page 2). Therefore, the limitations of the claims are met by this reference.

Response to Arguments

13. The response filed on July 12, 2006 has been considered, however, is not fully persuasive. The objection over the Oath/Declaration remains because applicant, state that a new Oath/Declaration will be filed when an allowance notification is given. New grounds of objections have been instituted over the claims for the reasons stated above. In addition, note that the rejections of record under 35 U.S.C. 112, first paragraph remains for the reasons stated above and stated herein. Applicant's state that the claims have been amended to remove reference to dimers/trimers. It is further stated that "analysis of sequence identities is well understood by one of skill in the art...Consequently a person of skill in the art can readily envision the genus of sequences having at least 80% identity to the provided peptides". Applicant's also point to *Enzo Biochem. Inc., v. Gene-Probe Inc* (see pages 11-12 of the response). This argument is not persuasive, for example the cited prior art references teach the structure of the peptide claimed

with a 100% sequenced identity, however, does not assign the function claimed. Thus, the rejection remains.

Applicant state that "a patent need not teach, and preferably omits, what is well known in the art and cites for example, *United States v. Telectronics Inc.* and *In re Buchner* pertaining to the enablement rejection. This argument is not persuasive because the claims are directed to variants thereof of the claimed structure based on the recitation of at least 80% or 90% sequence identity. Neither the specification or claims establishes conserved regions in the sequence to provide guidance as to what modifications can be tolerated in the peptide. Applicant also state that "as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement... is satisfied. Applicant states that persons of skill in the art can utilize direct synthesis or recombinant technology to make the claimed peptides (see page 13). These arguments are not persuasive, because the recitation of functional language absent empirical evidence does not garner function. In addition, the skilled artisan is invited to make all the possible fragments/variants encompassed in the claim and then test the same for the desired activity, which would require undue experimentation. The art as cited of record demonstrates the unpredictability of modifying the protein's structure and the expectation of retaining the same function as the wild type, despite mutagenesis techniques. Thus applicant's arguments have been considered in full but are not persuasive.

On page 14 applicant argues that the art rejections of records (Qvist and Shriners) are obviated with the amendments made to the claims (removal of "comprising" from claim 1). This argument is not persuasive because claim 1 remains open, thus a sequence comprising SEQ ID

NO:3 as taught in the art reads on this claim. In addition, the recitation of 80 or 90% sequence identity in the claims read on any variant of the structure. Thus, the rejection remains.

Conclusion

14. No claims are allowable.

15. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr, can be reached at (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner 9/29/06

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER